UCSF Helen Diller Family Comprehensive Cancer Center

Who Needs Radiation Post-Neoadjuvant Therapy?

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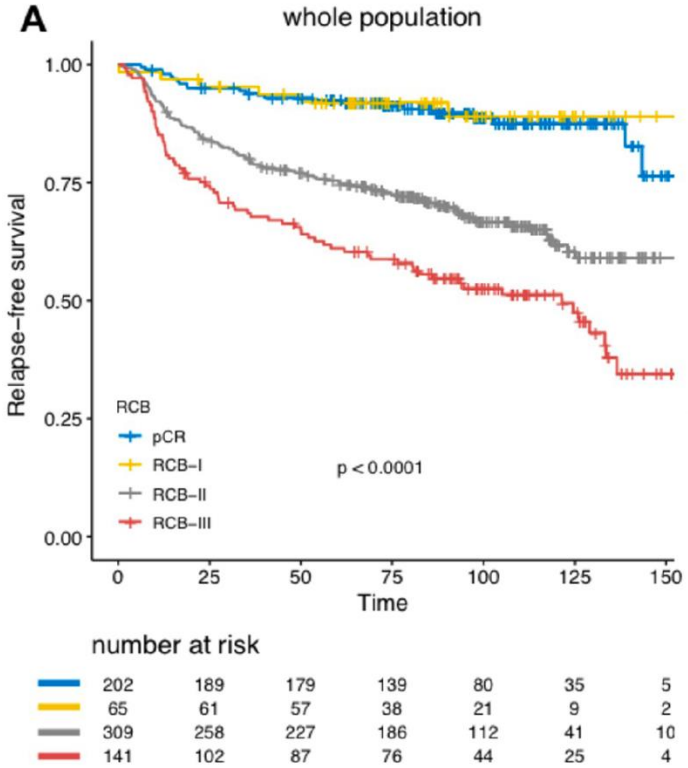
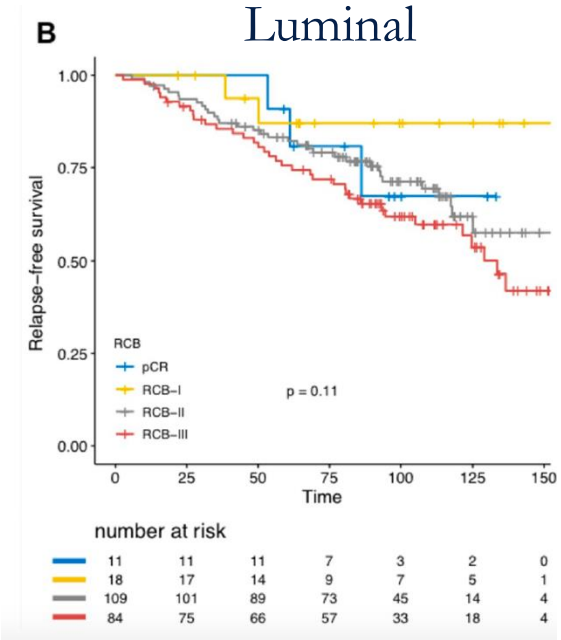
Learning Objectives

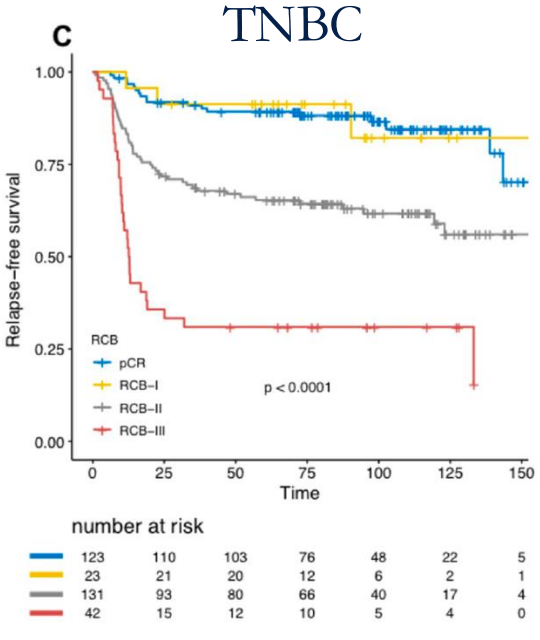
- Establish pCR after neoadjuvant chemotherapy (NACT) as a favorable clinical prognostic factor and residual disease as a negative clinical prognostic factor.
- Emphasize key components of workup to evaluate response to therapy and guide recurrence risk assessment.
- Recognize when post-NACT clinical trial data can be applied to guide radiotherapy management decisions.
- Balance historic data and modern studies for post-NACT radiotherapy decisions.

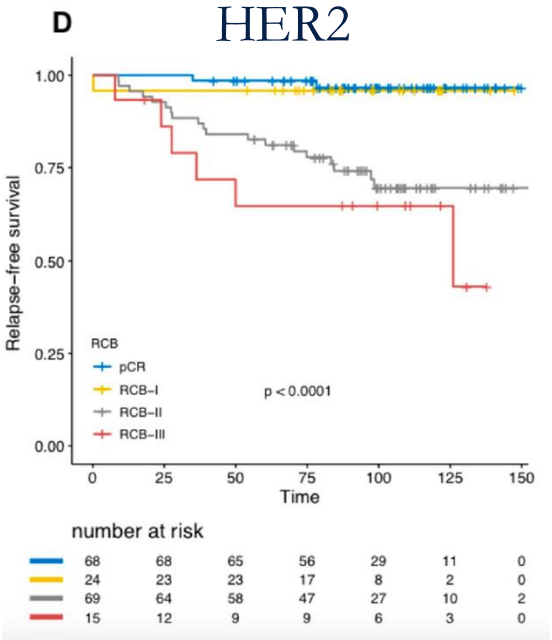
RCB is prognostic of oncologic outcomes



Hamy et al. PLOS One. 2020



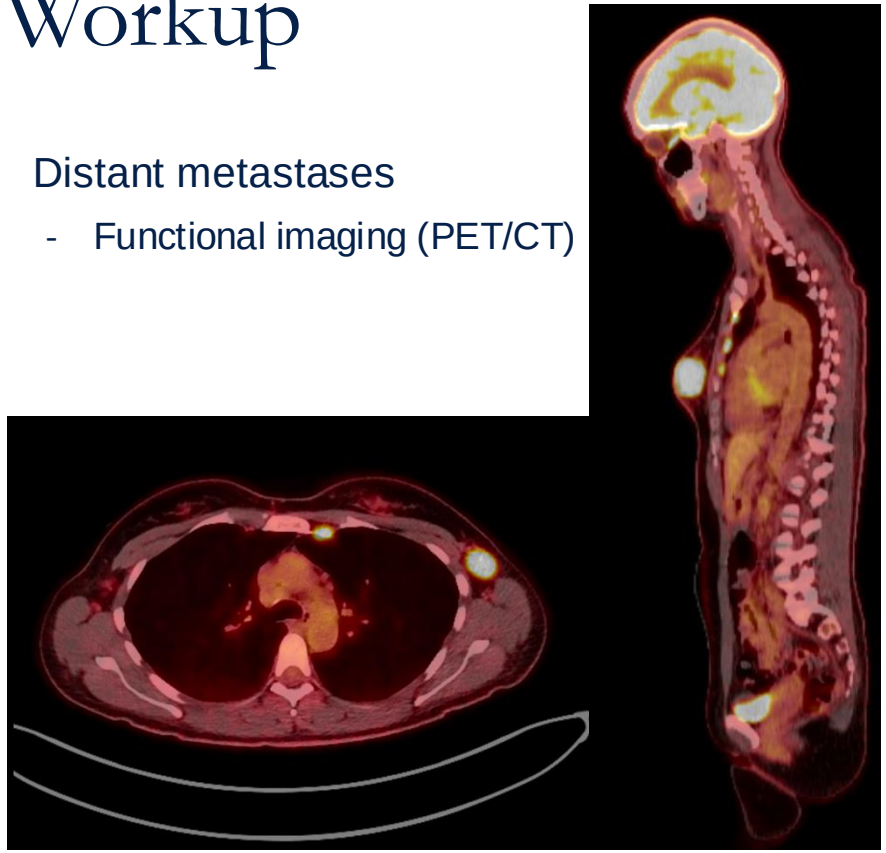




Hamy et al. PLOS One. 2020

Accuracy of Diagnostic Workup

- Primary tumor
  - Core biopsy (avoid vacuum assistance?)
  - Breast MRI (rule out multifocality/multicentricity)
- Regional lymph nodes
  - Breast MRI (evaluate nodal basins)
  - Nodal sampling:
    - Excise clipped node
    - Dual tracer
    - Sample 3 nodes (FNR <10%)
- Distant metastases
  - Functional imaging (PET/CT)



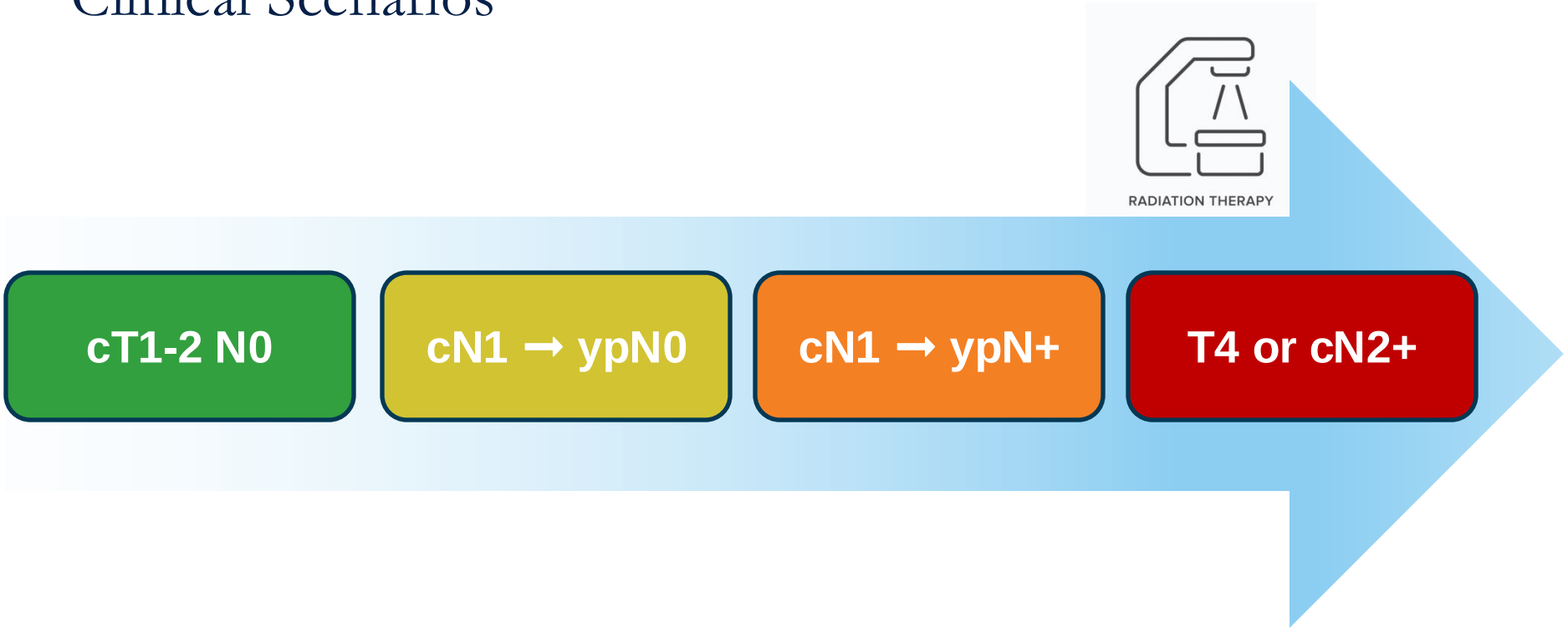
ACOSOG Z1071. JAMA Network. 2013
SENTINA Arm C. Lancet Oncol. 2013

Approach to radiation decision making

1. Using up front clinicopathologic information
   - Radiotherapy decision independent of in vivo response

2. Incorporating in vivo response
   - Opportunities for de-escalation and customization based on residual disease burden

Clinical Scenarios

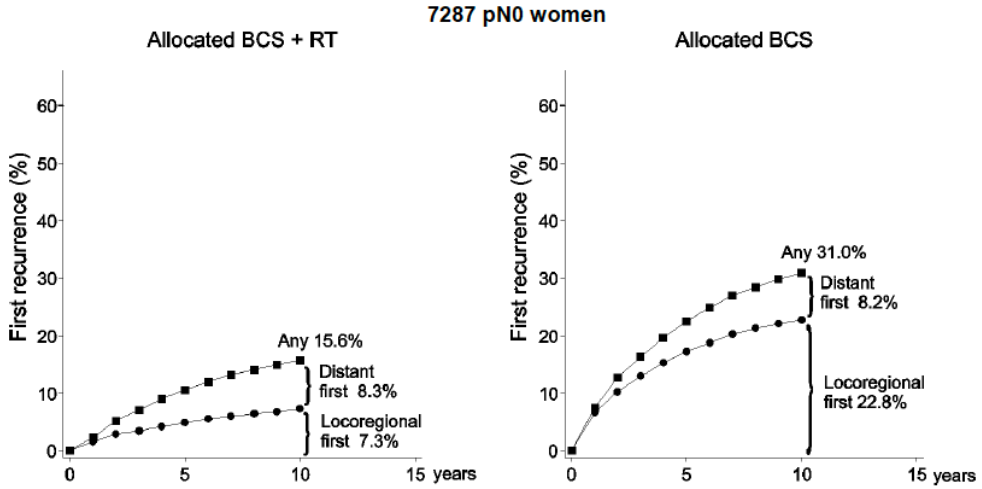


Early stage, node negative

cT1-2 N0

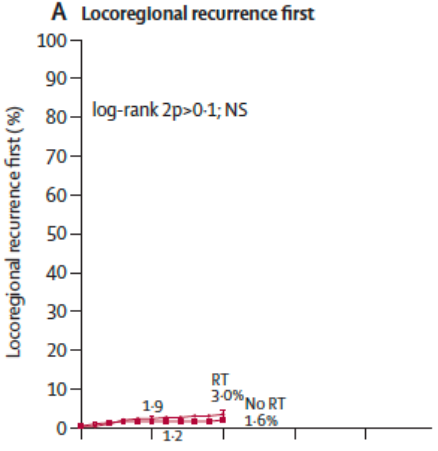
Post-BCS

- Adjuvant whole breast radiotherapy is the standard of care

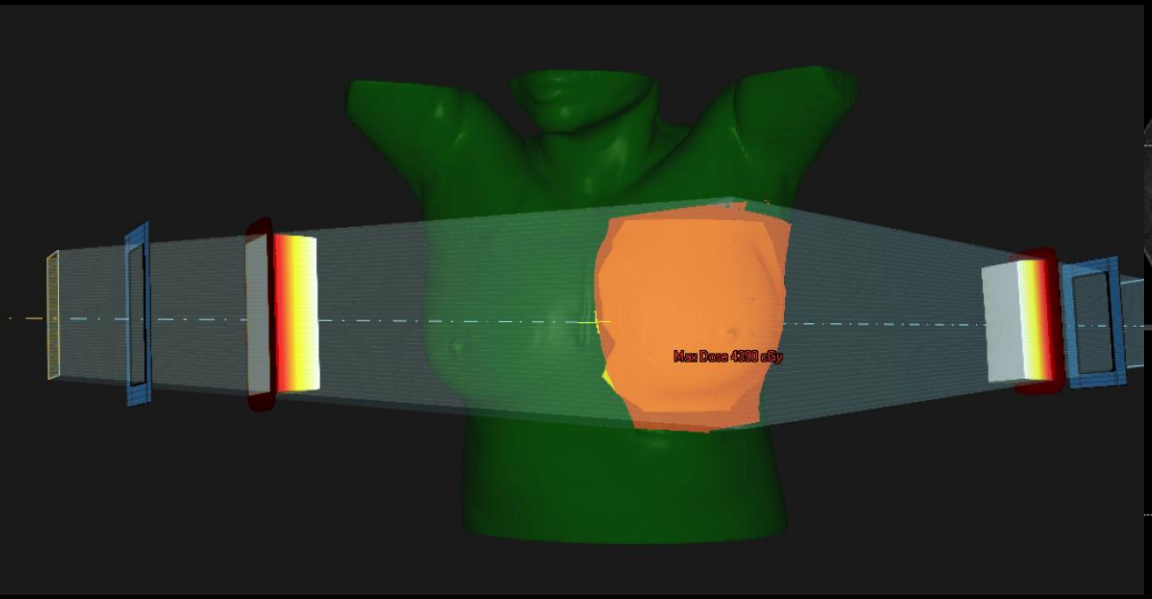


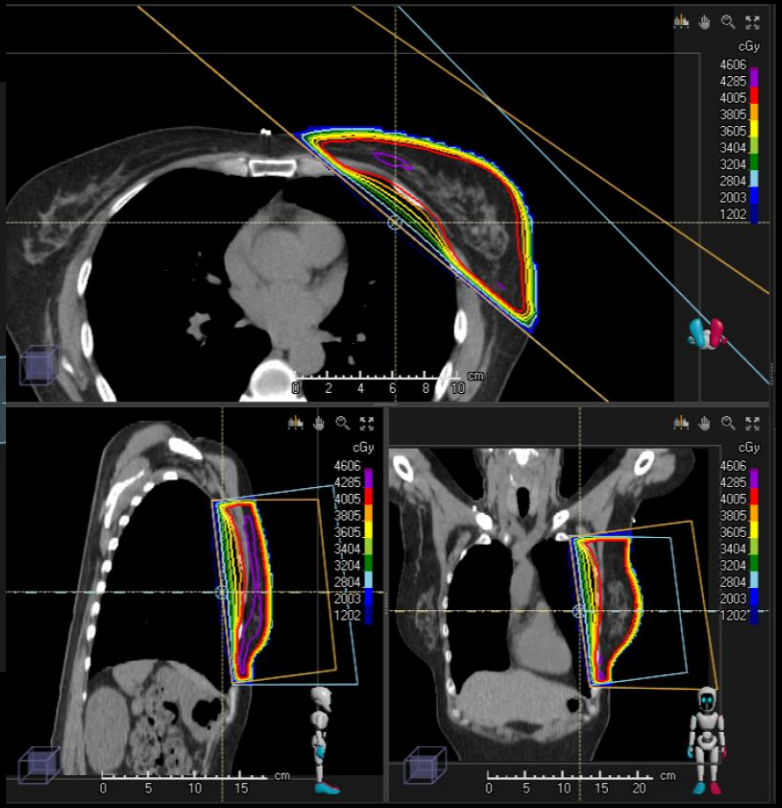
Post-Mastectomy

- No benefit from PMRT



EBCTCG. Lancet. 2011
EBCTCG. Lancet. 2014





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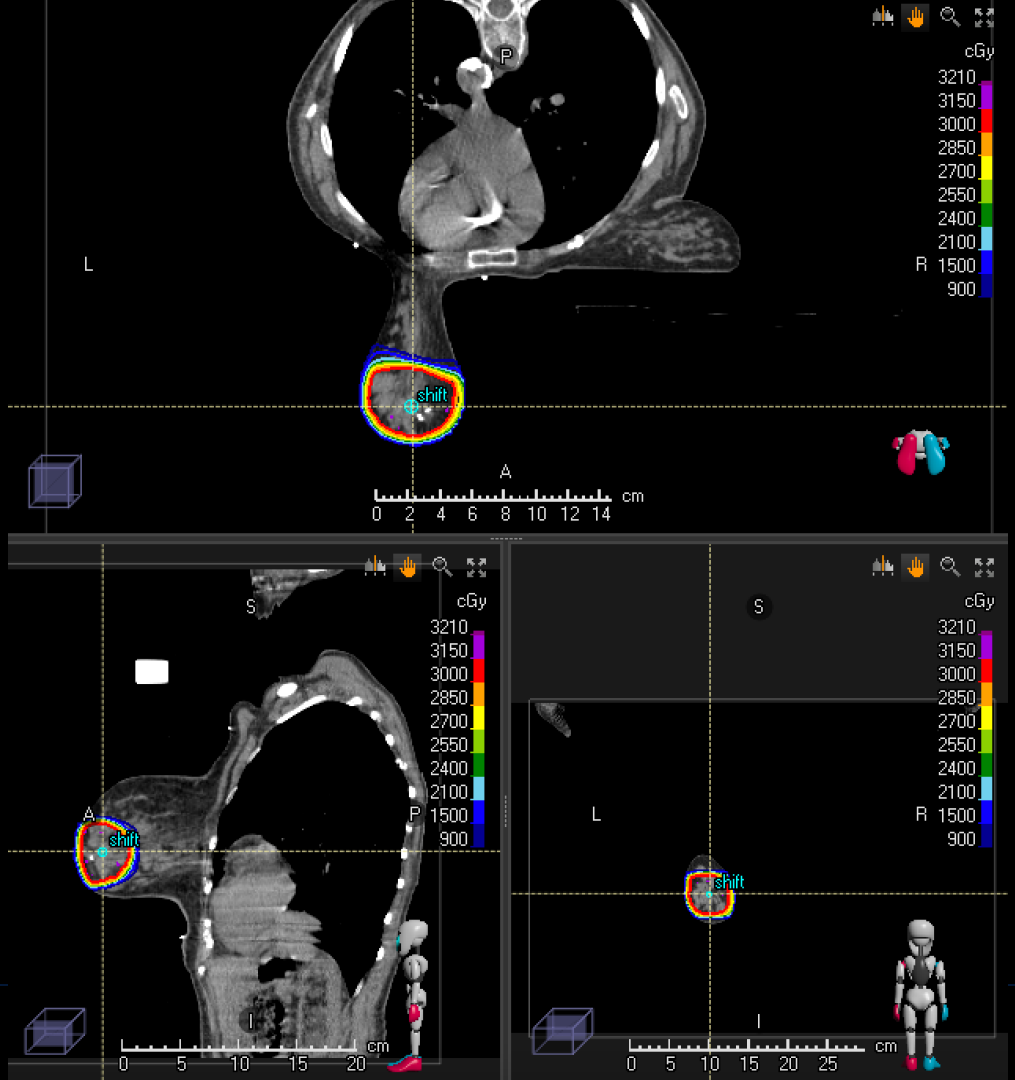
Partial breast irradiation trials

Study	N	Median Age (range)	Size	Node+	ER+	Her2+	G1-2	Median FU (years)	LR	Cosmesis
RAPID (50/25 or 42.5/16 vs 38.5/10 BID)	2135	61 [IQ 54-68]	71% <1.5 cm	<1%	91%	6%	84%	8.6	2.8% 3%	**PBI worse**
NSABP B39 (50/25 vs 38.5/10 BID)	4216	54 (38% <50)	58% <2 cm	10%	81%	---	63%	10.2	3.9% 4.6%	**PBI worse**
IMPORT-LOW (40/15 WBI vs PBI)	2018	62 (57-67)	1.2 cm (0.8-1.6 cm)	2-4%	95%	4%	90%	6.2	1.1% 0.5%	**PBI better**
Florence 50/25 vs 30/5 QOD	520	63 (40-85)	82-85% <2 cm	7-12%	95%	3-6%	87-90%	10.7	2.5% 3.7%	**PBI better**

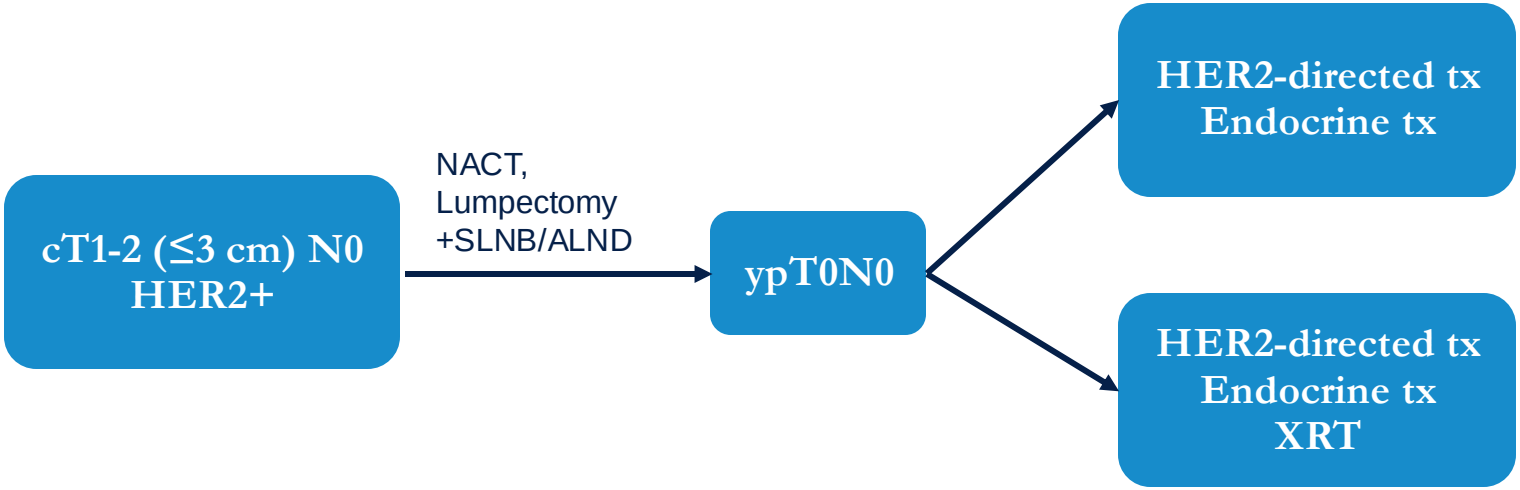


Partial breast irradiation appropriateness

Strongly recommend	Conditionally recommend	Conditional NOT recommend	NOT recommend
• Invasive G1-2 • Age≥40 • Size≤2cm(T1c) • DCIS G1-2	• Invasive G3 • ER- • Size >2 - ≤3cm • DCIS G3 • ILC • DCIS close margin	• Multiple higher risks • Her2+ w/o anti-Her2 tx • LVSI+	• Node+ • Margin+ • BRCA1/2

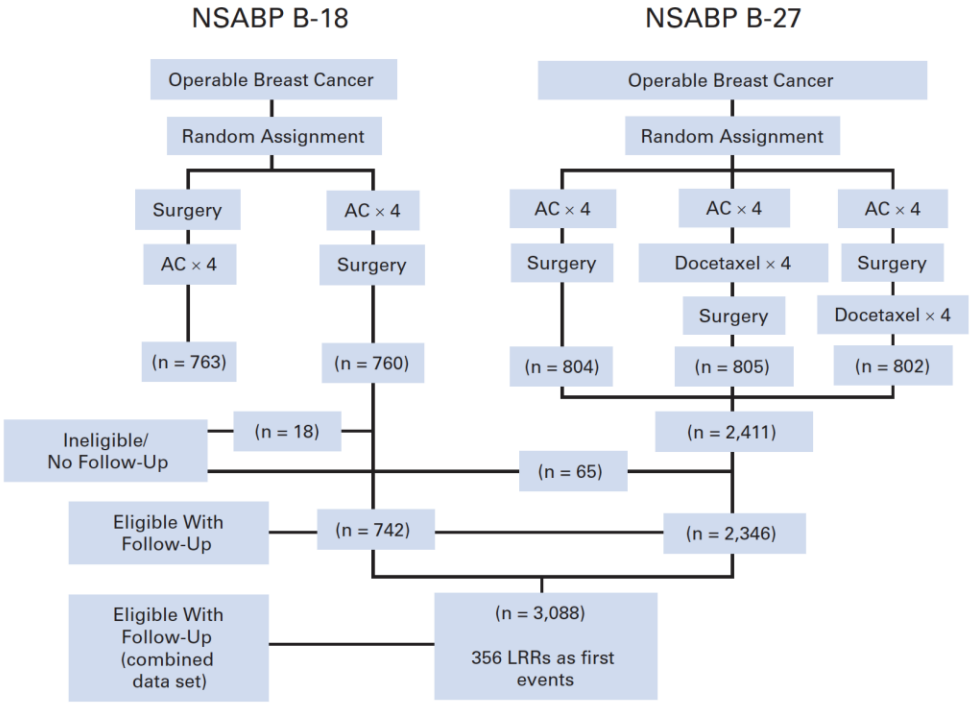
- There are NO randomized data to support de-escalation to PBI after NACT.

NRG BR008 (HERO) studying XRT omission



Early stage, node positive, responders

cN1 → ypN0



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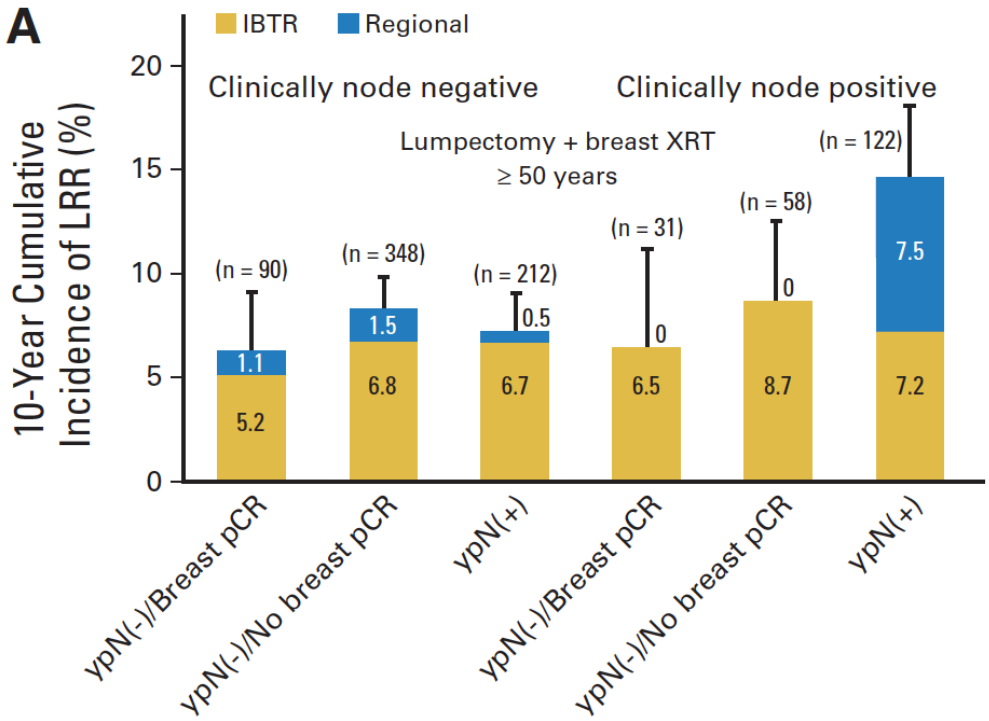
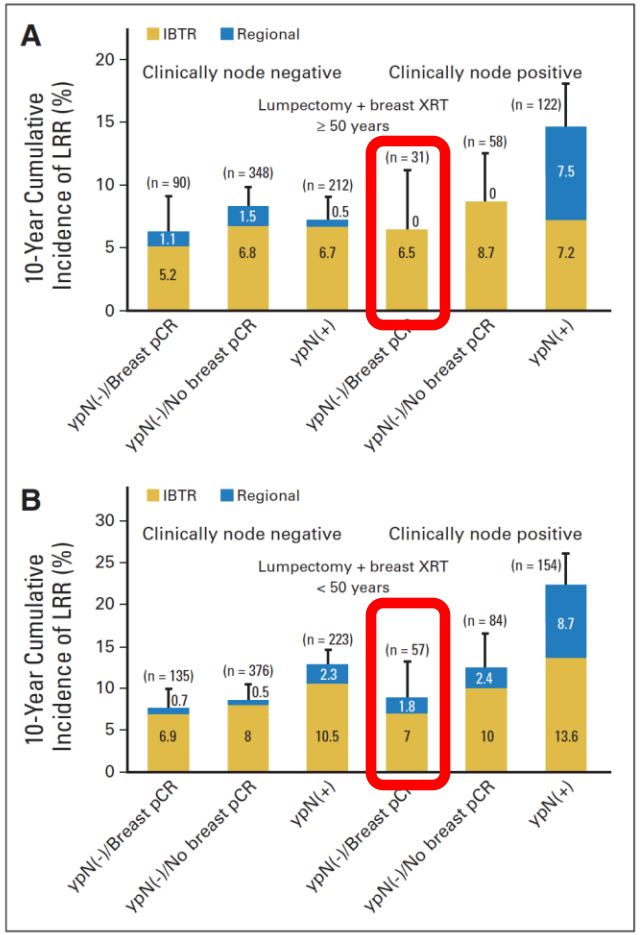
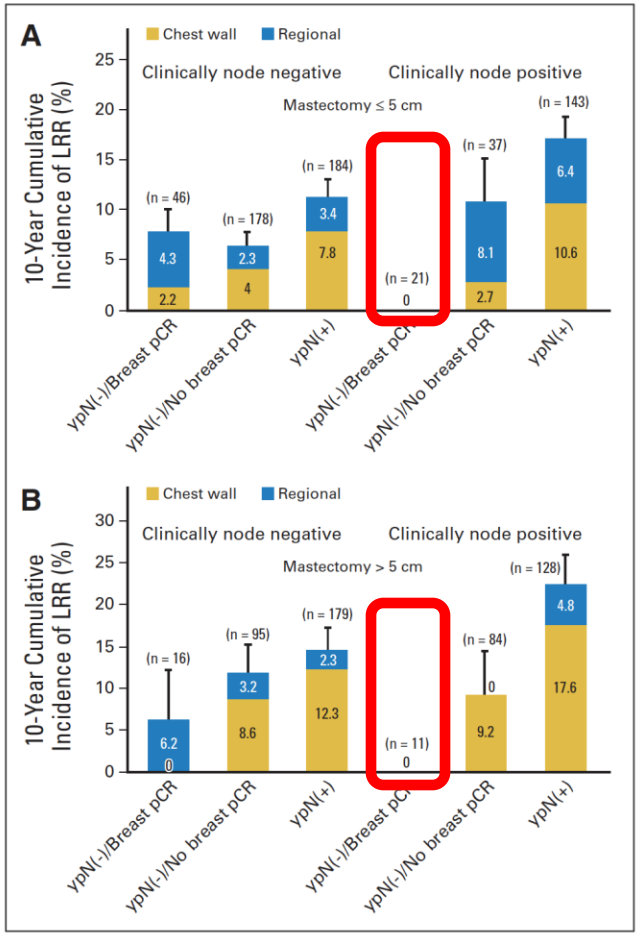
Mamounas. JCO. 2012

Low risk of regional recurrence after pCR



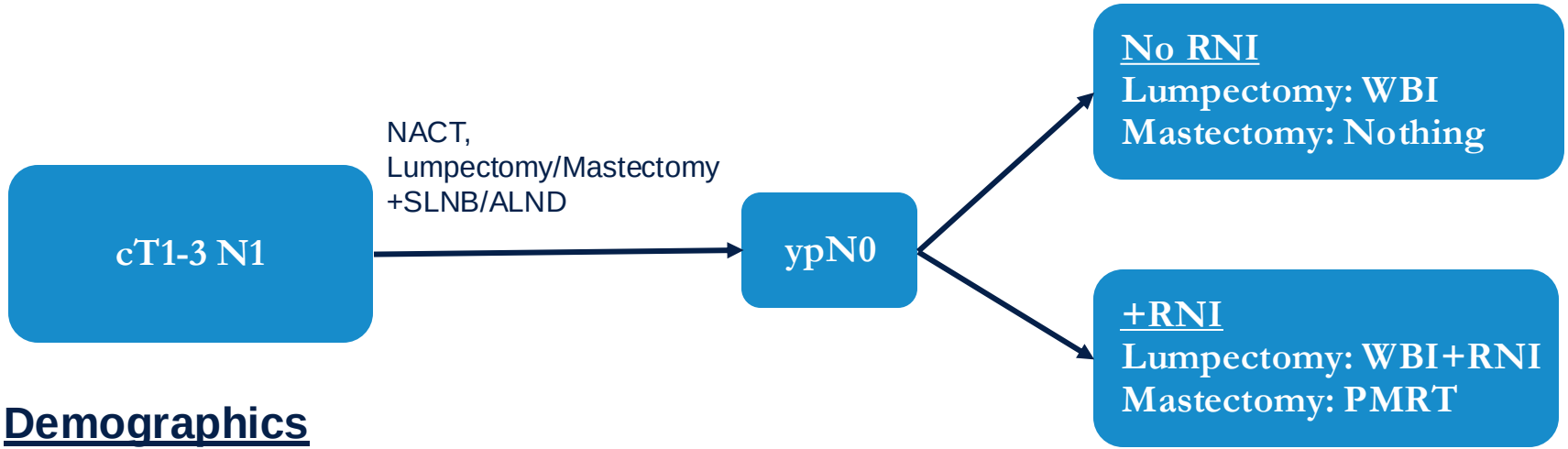
Mamounas. JCO. 2012





Mamounas. JCO. 2012

NSABP B51



Demographics

Age: ≤49 (40%), 50-59 (32%)
T: T1 (21%), T2 (60%)
Surgery: Lumpectomy (58%), SLNB (55%)
Subtype: TNBC (22%), HR+HER2- (21%), HR-HER2+(24%)
Breast pCR: 78%

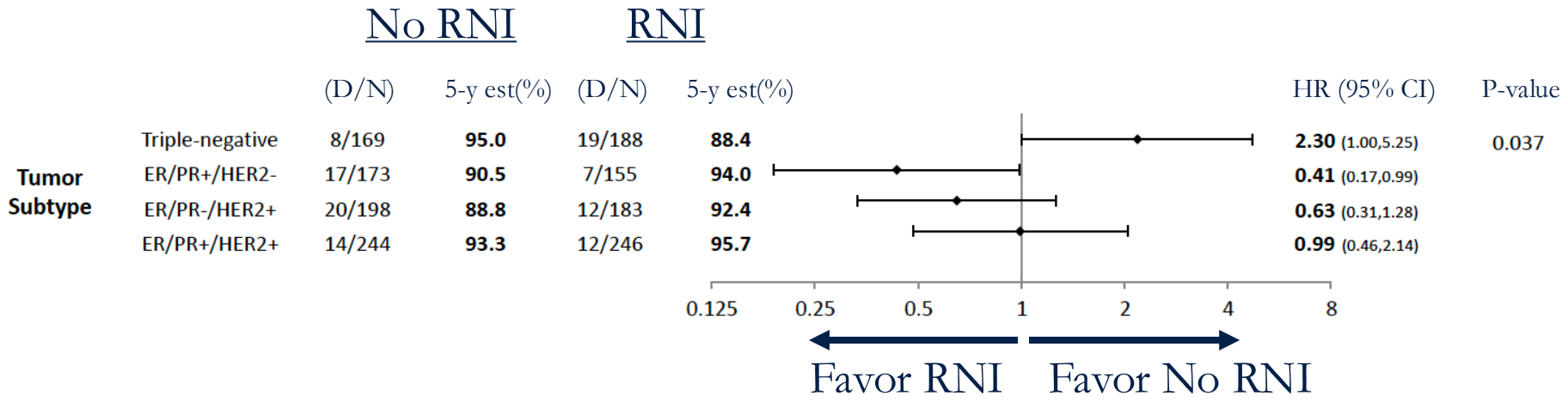
Mamounas. SABCS. 2023

NSABP B51 – no benefit to RNI after pCR

Outcome	No RNI	RNI	P-Value
Invasive Breast Cancer Recurrence-Free Survival	91.8%	92.7%	0.51
Isolated Locoregional Recurrence-Free Interval	98.4%	99.3%	0.09
Distant Recurrence-Free Interval	93.4%	93.4%	0.99
Disease-Free Survival	88.5%	88.3%	0.69
Overall Survival	94.0%	93.6%	0.59

Mamounas. SABCS. 2023

Invasive Breast Cancer Recurrence-Free Interval by Subtype

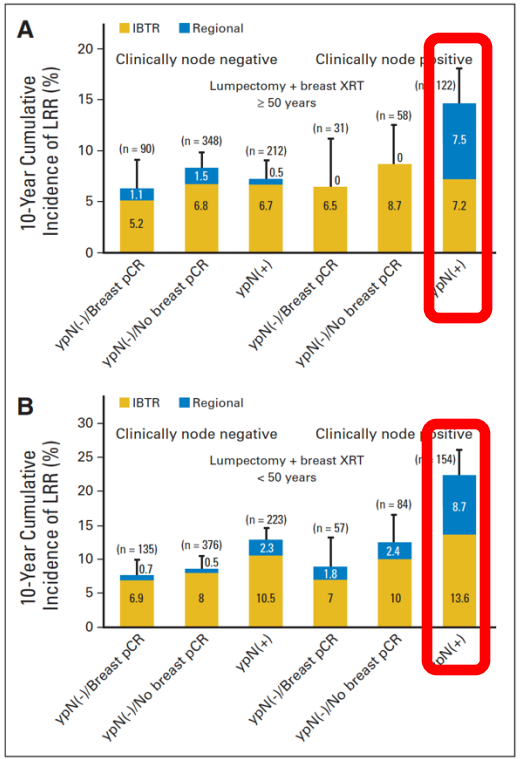


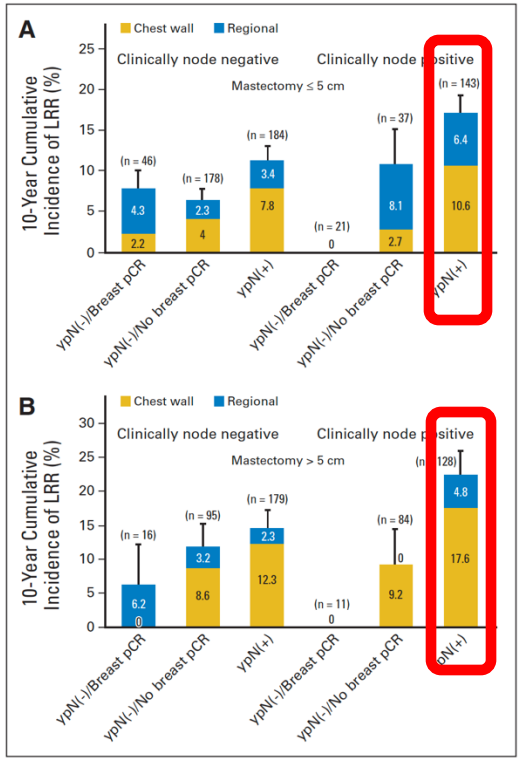
Mamounas. SABCS. 2023

Omission of RNI/PMRT after npCR

- Appropriate for T1-2N1
- Caution:
  - Young age
  - T3 tumor
  - Large residual in breast
  - Only 1 sampled node, especially if HR+
  - Higher clinical stage (e.g. cN2+)

Residual nodal disease carries highest risk of recurrence





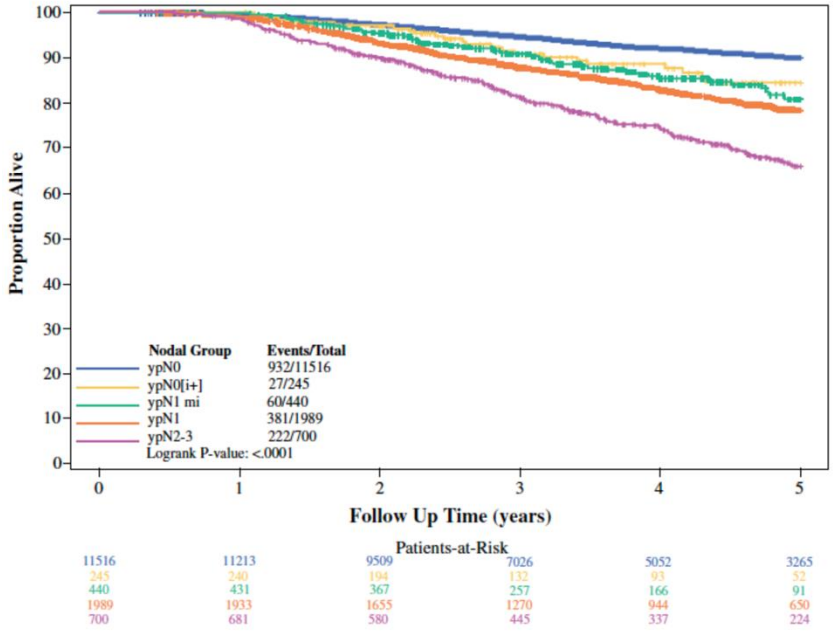
cN1 → ypN+

Mamounas. JCO. 2012

Any residual nodal disease has worse survival

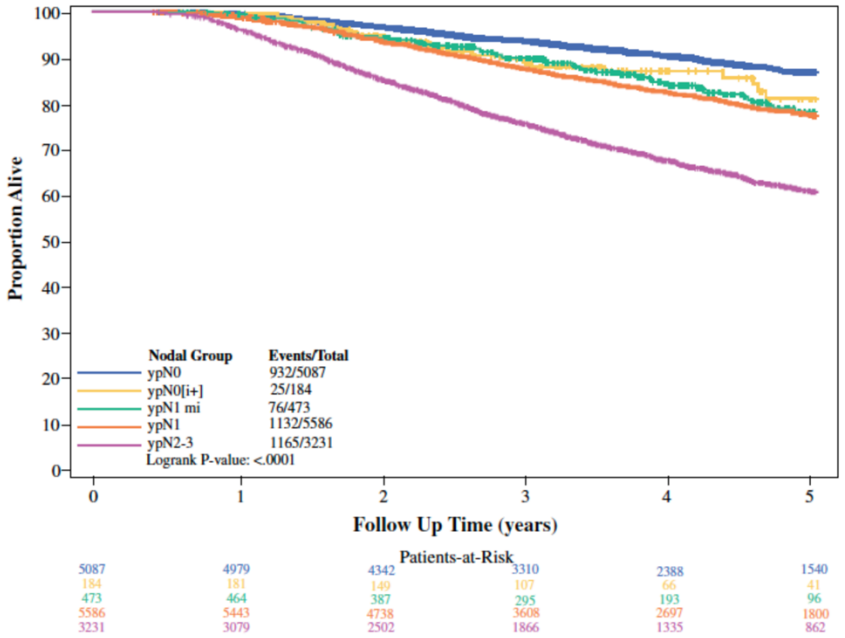
A

cN0 → ypN+



B

cN1 → ypN+



Wong et al. Ann Surg Oncol. 2019

Locoregional recurrence-free survival decreases with residual nodal burden

Pathologic nodal status	Total no. of patients	5-Year locoregional recurrence-free survival (LRRFS)		
		No. events/no. at risk at 5 years	LRRFS	(95% CI)
ypN0	524	19/286	95.7	(93.2–97.2)
ypN0[i+]	27	1/13	95.2	(70.7–99.3)
ypN1mi	61	2/30	96.6	(87.0–99.1)
ypN1	221	16/90	90.8	(85.3–94.3)
ypN2–3	134	17/50	84.3	(75.6–90.0)

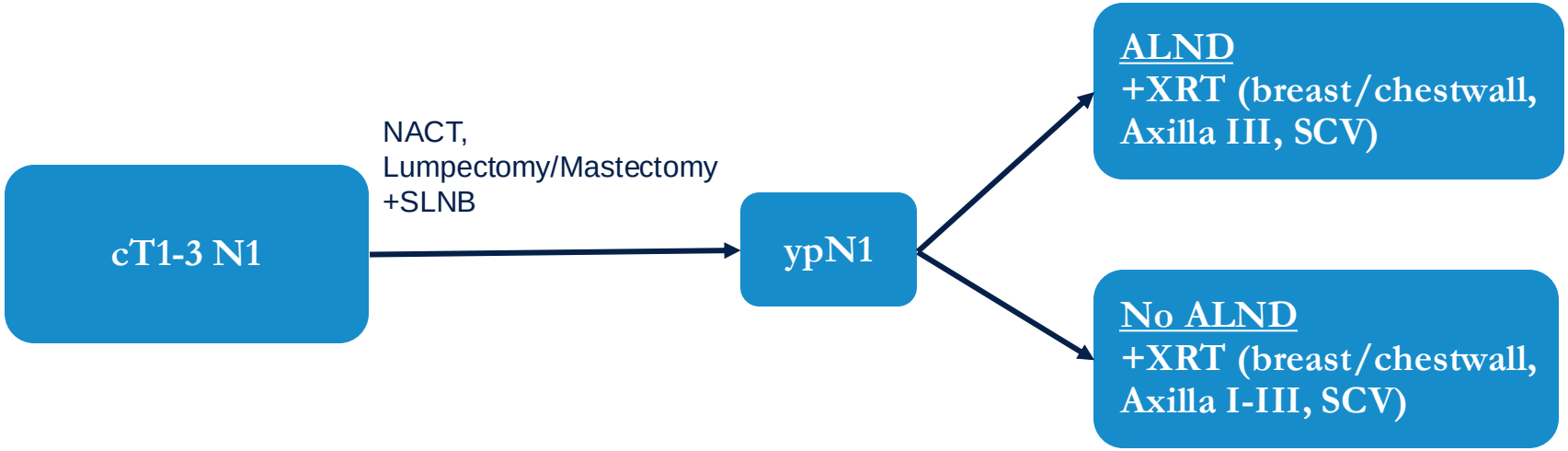
Wong et al. Ann Surg Oncol. 2019

Any residual nodal disease has worse DFS despite XRT

Characteristic	DFBWCC Adjusted HR (95% CI)*
	DFS
Pathologic nodal status	
ypN0	Ref
ypN1[i+]	**2.36 (1.01–5.51)**
ypN1mi	**2.14 (1.20–3.81)**
ypN1	**3.13 (2.15–4.57)**
ypN2–3	**4.43 (2.95–6.63)**
Breast pCR	
Yes	Ref
No	**2.44 (1.55–3.82)**
Biologic subtype	
HR+/HER2−	Ref
HR+/HER2+	0.97 (0.66–1.43)
HR−/HER2+	1.13 (0.65–1.96)
TNBC	**2.56 (1.83–3.57)**
Adjuvant radiation	
No	Ref
Yes	0.76 (0.46–1.26)

Wong et al. Ann Surg Oncol. 2019

Alliance A011202 – guide ypN1 axillary management

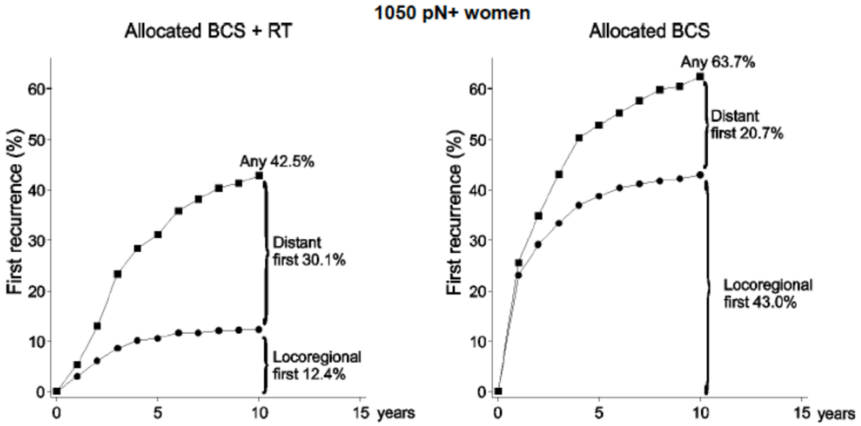


Locally advanced, node positive

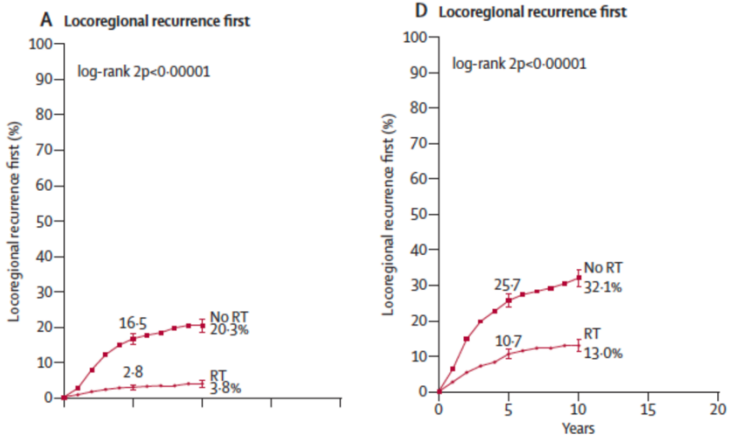
T4 or cN2+

- Advanced stage disease was not included in trials of XRT de-escalation after pCR.
- Adjuvant radiotherapy to the breast/chest wall and regional nodes remains the standard of care.

Post-BCS

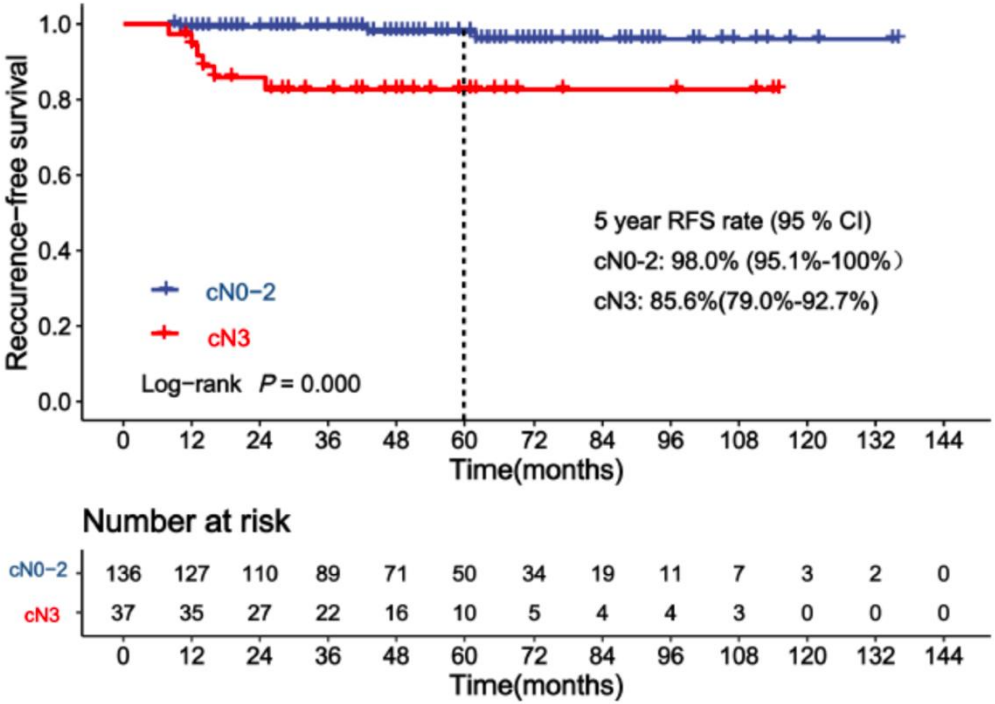


Post-Mastectomy



EBCTCG. Lancet. 2011
EBCTCG. Lancet. 2014

cN3 carries worse recurrence despite pCR



Qian et al. Frontiers in Onc. 2019

Conclusions

- Complete pathologic response to NACT portends lower chance of recurrence and improved survival.
- Residual nodal disease after NACT portends worse locoregional recurrence and survival.
- Diagnostic work-up to guide XRT decision making includes breast MRI, sampling at least 3 sentinel nodes, and radiographic evaluation of nodal basins.
- Recognize when post-NACT clinical trial data can be applied to guide radiotherapy management decisions.
- XRT management decisions balance up front clinicopathologic features with in-vivo treatment response (where supported by RCTs).

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